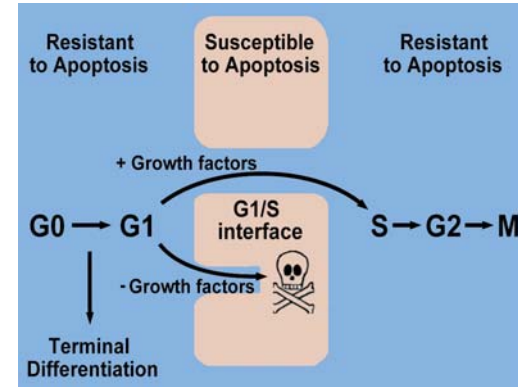


# Apoptosis in Ovarian Cells

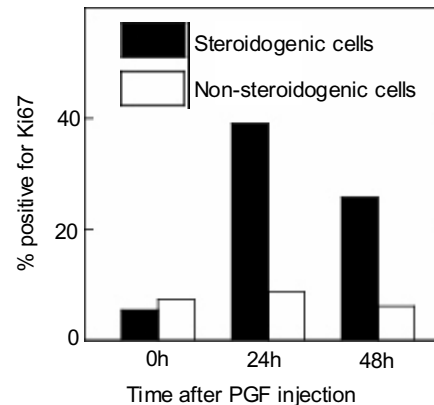
Most ovarian follicles that begin to grow and develop fail to reach ovulatory status but instead degenerate by apoptosis (programmed cell death) of follicular cells. Similarly, the corpus luteum undergoes regression at the end of its functional lifespan by apoptosis of luteal cells. The layer of epithelial cells that covers the surface of the ovary (ovarian surface epithelial cells, or OSE) also turn over by apoptosis and proliferation. A goal of the lab is to define factors controlling the susceptibility of ovarian cells to apoptosis. Our recent work suggests that quiescent or differentiated cells are relatively resistant to apoptosis as are rapidly proliferating cells. However, cells that begin to proliferate but lack growth factors to maintain proliferation are susceptible to apoptosis.



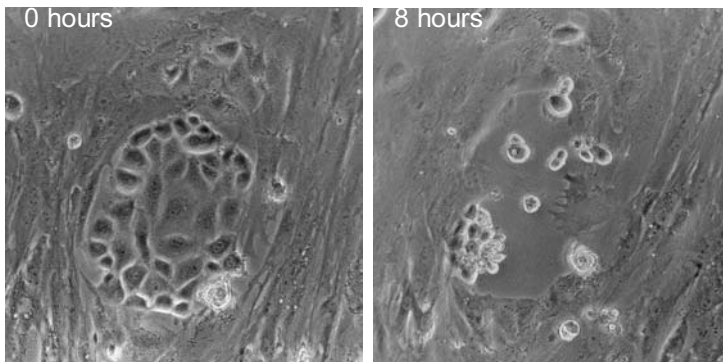
Model depicting the relationship between the stage of the cell cycle and susceptibility of ovarian follicle cells to apoptosis. Granulosa cells of the follicle undergo apoptosis predominantly at the transition from G1 to S phase. The effect of growth factors to protect against apoptosis in vitro is associated with their ability to promote G1-to-S progression and is prevented when that progression is blocked. G0 = resting phase, G1= early proliferative stage, S = DNA synthesis phase; G2 = pre-mitotic phase; M = mitotic phase.

## Regression of the Corpus Luteum

Experiments are being conducted using bovine corpora lutea to test the hypothesis that luteal cells undergo apoptosis coincident with their entry into an aberrant cell cycle.



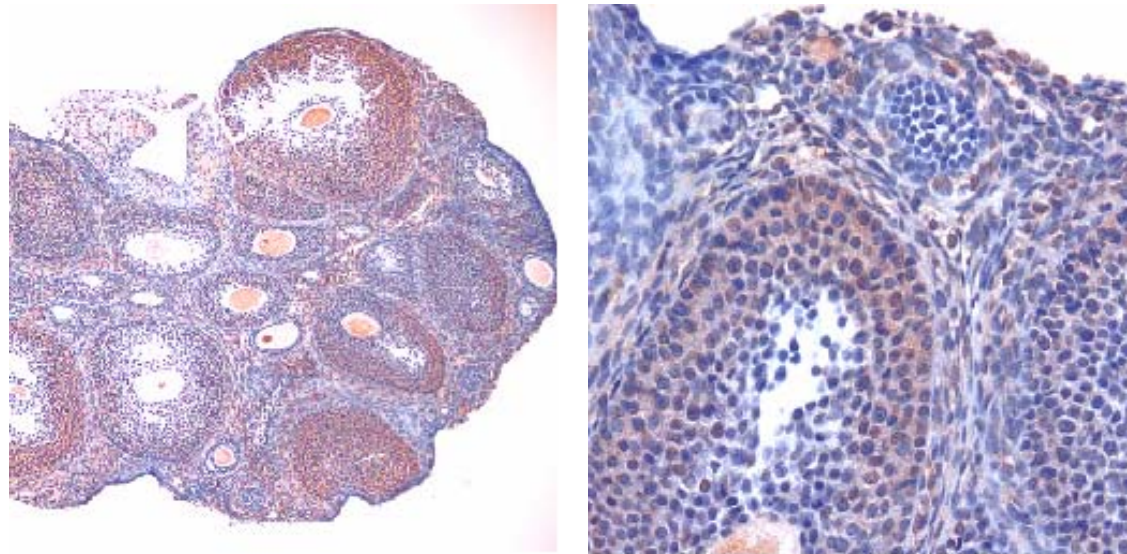
Expression of the cell proliferation marker, Ki67, by steroidogenic luteal cells increases during luteal regression. Luteal regression was initiated by injection of cows with prostaglandin (PG) F2a and CL were isolated at various times thereafter. Ki67 staining is elevated within 24 h in steroidogenic luteal cells but not non-steroidogenic cells of the CL (endothelial cells and fibroblasts). The cell cycle is not completed and these cells undergo apoptosis.



Cultured OSE undergo apoptosis mediated by binding of Fas ligand to its receptor. The cobblestone-appearing patches of OSE degenerate after treatment with Fas ligand.

## *Hedgehog Signaling in the Ovary*

The hedgehog family of secreted proteins regulates development in the embryo and in a wide array of adult tissues. Hedgehog signaling is essential for ovarian function in *drosophila*, but it has not been studied previously in the mammalian ovary. Mutations in components of the hedgehog pathway have been implicated in a variety of cancers. We are investigating the role of the hedgehog pathway in ovarian follicle development. In addition, we are studying the role of the pathway in the proliferation and turnover of the OSE, the cell type that most frequently gives rise to ovarian cancer. One approach that we are using is to create several strains of mice with conditional deletions of the hedgehog receptor gene in order to determine the role of the pathway in the early development of the ovary as well as in the adult animal.



Immunohistochemistry using an antibody that detects hedgehog proteins. Granulosa cells of multi-layered follicles stain positively (red color). At right is a higher magnification showing part of an individual follicle.